A NOVEL *AIRE* GENE MUTATION IN TWO SIBLINGS REVEALING DIFFERENT PHENOTYPES OF AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE 1

Melek Yıldız[1], Banu Aydın[1], Alper Gezdirici[2], Hasan Önal[1]

[1]Division of Pediatric Endocrinology, [2]Division of Genetics, Kanuni Sultan Süleyman Training and Research Hospital, Istanbul, Turkey

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Introduction

Autoimmune polyendocrine syndrome type 1 (APS-1) is a rare autoimmune disease characterized by chronic mucocutaneous candidiasis, hypoparathyroidism and primary adrenal insufficiency. Minor components of the disease are diverse among patients, even within the same family.

APS-1 is autosomal recessively inherited and caused by biallelic mutations in the autoimmune regulator (AIRE) gene.

Aim: To define different clinical and laboratory characteristics of two affected siblings diagnosed as APS-1 with the same genetic cause.

Case 1, *14 3/12 year-old girl*

Natal-Postnatal: Born to consanguineous parents with a birth weight of 3300 grams after an uneventful term pregnancy.

3$^{7/12}$ year-old: Referred due to tetany.

•Normal growth.

•Hypocalcemia, hyperphosphatemia and low PTH levels

•Diagnosis: Hypoparathyroidism.

•Treatment: Calcitriol + Calcium

12$^{6/12}$ year-old: Short stature

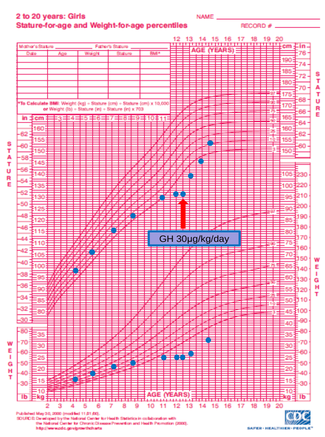
•↓ Annual growth rate (4cm/y), Bone age: 9 year

•Karyotype: 46,XX

•↓ IGF-1and ↓ IGF-BP3

•GH stimulation tests, with priming:

- L-dopa GH peak: 3.54 ng/ml
- Clonidine GH peak: 2.75 ng/ml



•Pituitary MRI: Normal

•Diagnosis: GH deficiency

•Treatment: GH

14 year-old: Physical examination: Weight: 34.2 kg (-3.62 SDS), Height: 151 cm (-1.65 SDS), BMI: 15 (-3.16 SDS). Normal mental motor development, dental enamel hypoplasia, fragile nails, malabsorptive symptoms. Pubic hair and breast development consistent with Tanner stage II.

Laboratory: Hypochromic microcytic anemia (Hb 8.7g/dl, MCV 60.5), Normal vit B12, Normal Ca-P, Normal TFT, Negative thyroid autoantibodies, Negative coeliac autoantibodies, Normal PRL, normal cortizol and FSH/LH.

Urinary USG: Bilateral medullary nephrocalcinosis

Case 2, *9-year-old boy*

Natal-Postnatal: Born with a birth weight of 3750 grams after an uneventful term pregnancy.

4$^{2/12}$ year-old: Referred due to tetany.

- Normal growth.
- Hypocalcemia, hyperphosphatemia and low PTH levels
- Diagnosis: Hypoparathyroidism.
- Treatment: Calcitriol + Calcium

7 year-old: Ectodermal dystrophy of the nails and total alopecia areata.

9 year-old: Physical examination: Weight: 36.2 kg (1.18 SDS), Height: 133.3 cm (0.1 SDS), BMI: 20.3 (1.43 SDS). Normal mental motor development, ectodermal dystrophy of the nails and total alopecia areata. Puberty consistent with Tanner stage I.

Laboratory: Normal Ca-P, Normal TFT, Negative thyroid autoantibodies, Negative coeliac autoantibodies, Normal PRL, normal cortizol and FSH/LH.

Urinary USG: Normal

Table 1. Disease components of the siblings with APS-1

	Case 1 ♀	Case 2 ♂
Main components		
Chronic mucocutaneous candidiasis	+	+
Hypoparathyroidism	+	+
Primary adrenal insufficiency	-	-
Minor components		
Hypo/Hyperthyroidism	-	-
Type 1 DM	-	-
Hypogonadism	-	-
Alopecia universalis	-	+
Dental enamel hypoplasia	+	-
Vitiligo	-	-
Ectodermal dystrophy	-	+
Malabsorption	+	-
Autoimmune hepatitis	-	-
Pernicious anemia	-	-
Growth hormone deficiency	+	-
AIRE mutation (c.464-3 C>G)	homozygous	homozygous

Conclusion

This is the first report of the variation in AIRE gene, which is referred as c.464-3 C>G, resulted in different phenotypes of APS-1 in two siblings. Diverse findings can appear over time. Here we also report isolated growth hormone deficiency as an unusual finding of APS-1.

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